REMARKS

The present application is directed to methods for detecting cancer-associated marker proteins. Prior to the current amendment, Claims 1-4, 20-22, 30-33, 50 and 51 were pending in the present application. Claims 20-22, 30-33, 50 and 51, withdrawn from consideration by the Examiner as drawn to non-elected inventions, are hereby cancelled by the applicants. Upon entry of the current amendment, Claims 1-4 will be pending in the present application. Reexamination and reconsideration of the application are requested in view of these amendments and the following remarks.

Specification

The Examiner objects to the disclosure because Figure 1 depicts an amino acid sequence without an appropriate sequence identifier (SEQ ID NO). To obviate the objection and in accordance with the Examiner's recommendation, applicants respectfully request the Examiner's approval of the amendment to incorporating SEQ ID NO:1 into Figure 4. The amendment is shown in red in compliance with 37 CFR §1.121(d) and does not introduce any new matter. Applicants respectfully assert that the amendment overcomes the rejection and request that the objection to the disclosure be withdrawn.

Priority

Applicants will file a certified copy of the prior Great Britain's patent application No. GB 9827228.9 filed December 10, 1998, as required by 35 U.S.C. §119(b).

Claim Rejections under 35 U.S.C. §112, second paragraph

The Examiner rejects Claim 2 under 35 U.S.C. §112, second paragraph, as indefinite. The Examiner asserts that the term "substantially asymptomatic for pre-neoplasia or cancer" is unclear and assumes that the term denotes a benign tumor.

Applicants respectfully traverse the rejection. Applicants respectfully assert that the term "substantially asymptomatic for pre-neoplasia or cancer" has a well-defined meaning to one skilled in the art. Specifically, the term "substantially asymptomatic" is known to those skilled in the art as meaning the absence of symptoms of a disease or a condition according to the generally accepted clinical diagnostic criteria for the disease or the condition. The term "cancer" commonly denotes a malignant tumor of potentially unlimited growth that expands locally by invasion and systemically by metastasis or an abnormal bodily state, or a condition associated with such tumors. The term "pre-neoplasia" commonly denotes changes in a tissue, which are associated with an increased risk of subsequently developing cancer, for example, but not limited to, "borderline lesions," such as atypical ductal hyperplasia in a mammary gland, dysplasia of an oesophagus, or leukoplakia of an oral cavity. In contrast, the term "benign tumor," is known to mean a tumor that does not metastasize.

Applicants respectfully assert that the term "substantially asymptomatic for pre-neoplasia or cancer" in Claim 2 is definite and has a meaning of not exhibiting

symptoms of cancer or pre-neoplasia. In view of the foregoing, applicants respectfully request withdrawal of the rejection of Claim 2 under 35 U.S.C. §112, second paragraph.

Claim Rejections under 35 U.S.C. §103(a)

The Examiner rejected Claims 1-4 under 35 U.S.C. §103(a) as being obvious over either von Mensdorff-Pouilly *et al.* (1996) *Eur. J. Cancer.*, v. 32(A):1325-1331 (hereinafter referred to as *Mensdorff-Pouilly et al*), or Gourevitch *et al.* (1995), *Br. J. Cancer*, v. 72:934-938, (hereinafter referred to as *Gourevitch et al.*) in view of Petrarca *et al.* (1996) *Eur. J. Cancer*, 1996, v. 32:1(12):2155-2163 (hereinafter referred to as *Petrarca et al.*).

Applicants respectfully traverse the rejection.

Mensdorff-Pouilly et al. and *Gourevitch et al.* teach detection of circulating **immune complexes** containg polymorphic epithelial mucin (PEM) encoded by MUC-1 in sera of patients with various stages of cancer. The **complexes** are detected in the patients' sera using monoclonal antibodies to polymorphic epithelial mucin. *Petrarca et al.* teaches generation of human MUC-1 antibodies by B-cell lines derived from cancer patients. The Examiner asserts that it is obvious to derive the method of detecting cancer-associated proteins, particularly MUC-1, as claimed in Claims 1-4, by replacing the monoclonal antibodies in the teachings of *Mensdorff-Pouilly et al.* and *Gourevitch et al.* with a MUC-1 autoantibody taught in *Petrarca et al.*

The present application claims a cancer-associated marker detection method that utilizes autoantibodies. Applicants respectfully submit that the method as claimed in Claims 1-4 of the present application cannot be derived by combining the teachings of *Mensdorff-Pouilly et al.* or *Gourevitch et al.* with the teachings of *Petrarka et al.*

Applicants respectfully bring to the Examiner's attention that *Mensdorff-Pouilly et al.* and *Gourevitch et al.* fail to teach detection of a cancer-associated marker protein, particularly, MUC-1, *per se*. Both *Mensdorff-Pouilly et al.* and *Gourevitch et al.* teach detection of **immune complexes,** or complexes of autoantibodies with the MUC 1 antigen (see, for example, p. 1326, first column, second paragraph, last sentence in *Mensdorff-Pouilly et al.*) using murine monoclonal antibodies (mAbs). That is, mAbs taught in *Mensdorff-Pouilly et al.* and *Gourevitch et al.* **bind to the immune complex** containing MUC-1. Therefore, *Mensdorff-Pouilly et al.* and *Gourevitch et al.* fail to teach or suggest the method of the present invention as claimed in Claims 1-4, because they fail to teach detection of MUC-1 as such.

Further, for the binding of the murine mAb to the immune complex to occur, murine mAbs must bind to a different epitope of MUC-1 than the autoantibodies of the claimed method. Therefore, murine mAbs used in *Mensdorff-Pouilly et al.* and *Gourevitch et al.* are not replaceable by the human antibodies taught in *Petrarca et al.*, and are not their functional equivalents, as suggested by the Examiner, because epitopes to murine mAbs taught in *Mensdorff-Pouilly et al.* and *Gourevitch et al* are clearly different from the autoantibody epitopes utilized in the claimed method.

The Examiner asserts that *Petrarca et al.* teaches on page 2161, last two paragraphs, that MUC-1 autoantibody is a functional equivalent of the murine mAb used in *Gourevitch et al.* and *von Mensdorff-Pouilly et al.* Applicants respectfully disagree. In the cited passage, *Petrarca et al.* generally infers that "human auto-antibodies are capable of successfully binding to tumor cells as well as to a circulating antigen, since PEM immunocomplexes have been described in breast cancer patient sera." Indeed, *Petrarca et al.* teaches binding of human B-cell derived antibodies to peptide epitopes and to cancer cells. However, *Petrarca et al.* fails to teach or suggest binding of the human B-cell derived antibodies to cancer-associated MUC-1 protein circulating in the serum. *Petrarca et al.* also fails to teach or suggest that an isolated **autoantibody** can be used as a diagnostic reagent for detection of the circulating antigen in a bodily fluid sample.

In fact, *Petrarca et al.* teaches away from using human B-cell derived antibodies as a cancer-detection agent. For example, in the passage cited by the Examiner, *Petrarca et al.* discusses weak reactivity observed for the B-cell derived antibodies and recognizes that these antibodies were generated to cross-reactive (rather than cancer-specific) epitopes. Testing of the activity of the human anti-MUC-1 autoantibodies by cytofluorometric analysis in *Petrarca et al.* demonstrated different reaction of the autoantibodies with MUC-1-expressing cancer cell lines, ranging from negative to weakly positive (see page 2161, first paragraph, and page 2158, second column, bottom, referring to Figure 2). While the isolated human antibodies disclosed in *Petrarca et al.* are capable of recognizing tumor cells, albeit weakly, there is no teaching or suggestion in *Petrarca et al.* of

isolated human autoantibodies capable of recognizing circulating MUC-1 antigen in samples of patients' serum.

Petrarca et al. also explicitly teaches away from the B-cell derived anti-MUC-1 autoantibodies disclosed therein being equivalent to monoclonal anti-MUC-1 antibodies, such as those used in *Gourevitch et al.* and von *Mensdorff-Pouilly et al.* For example, *Petrarca et al.* teaches epitope mapping of human anti-MUC-1 antibodies and concludes that the epitopes recognized by these antibodies are different from the antigenic determinants dominant in mice. All of the human antibodies include the sequence PPAH in their epitopes, whereas the epitope immunodominant in mice is PDTR.

The Examiner asserts that "when one could not find the monoclonal antibody in the stock freezer but can find the MUC-1 autoantibody, and one has to get the result of whether one has the circulating antigen before the next shipment of the monoclonal antibody arrives, one having ordinary skill in the art, at the time the claimed invention [was made] would have been motivated to use the MUC-1 autoantibody to detect the circulating MUC-1 antigen with reasonable expectation of success." Applicants respectfully assert that, based on the teachings of *Petrarca et al.*, one skilled in the art would be motivated **to not use** the MUC-1 autoantibody disclosed therein for detection of the serum cancer-associated MUC-1 antigen, one skilled in the art also would expect **to not succeed** in detection of the serum cancer-associated MUC-1 antigen with the autoantibodies taught in *Petrarca et al.*

In contrast, the applicants unexpectedly identified and disclosed in the present application human anti-MUC-1 autoantibodies that are sensitive and specific for the forms of MUC-1 protein present in the serum of cancer patients. Example 2 and Figures 1-2 of the present application teach the high specificity of autoantibodies isolated from cancer patients for MUC-1 present in the serum of patients with cancer. The autoantibodies show high specificity for cancer-associated MUC-1 and have almost no affinity for MUC-1 isolated from healthy individuals or from breast cancer cell lines. In addition, the affinity of the autoantibodies for MUC-1 protein associated with cancer is much higher than that measured for a murine monoclonal antibody. Example 3 further teaches the affinity of human autoantibodies for cancer-associated forms of MUC-1. Example 4 also teaches high sensitivity and specificity of the autoantibodies isolated from cancer patients, compared to mouse monoclonal antibodies, for detection of MUC-1 antigen in patients' sera.

In summary, *Mensdorff-Pouilly et al.* and *Gourevitch et al.* fail to teach or suggest the method of the present invention as claimed in Claims 1-4, because they do not teach detection of MUC-1 as such, but a detection of a MUC-1-autoantibody complex with a murine monoclonal antibody. Moreover, murine monoclonal antibodies taught in *Mensdorff-Pouilly et al.* and *Gourevitch et al.* bind to a different epitope than human autoantibodies. Human autoantibodies taught in *Petrarca et al.* also bind to a different epitope than murine monoclonal antibodies. Therefore, the autoantibodies and murine monoclonal antibodies taught in the cited references are not mutually replaceable. Further, *Petrarca et al.* teaches

away from using human autoantibodies disclosed therein for detection of serum cancer-related proteins.

In view of the foregoing, applicants respectfully assert that *Mensdorff-Pouilly et al.*, *Gourevitch et al.,* or *Petrarca et al,* separately or in any combination thereof, fail to teach, suggest, or provide motivation to derive the applicants' unexpected findings and the method of detecting a cancer-associated marker protein as claimed in Claims 1-4 of the present application. Applicants respectfully assert that *Mensdorff-Pouilly et al.*, *Gourevitch et al.,* or *Petrarca et al,* separately or in any combination thereof, fail to teach, suggest, or provide motivation to derive the applicants' invention as claimed in Claims 1-4, and fail to render the applicants' invention obvious. Applicants respectfully assert withdrawal of the rejection of Claims 1-3 under 35 U.S.C. §103(a).

CONCLUSION

This First Amendment and Response to the Non-Final Office Action is fully responsive. Applicants respectfully assert that the claims are now in condition for allowance and request that the application be passed to issuance. Applicants respectfully request that the Examiner contact the undersigned agent if any questions arise concerning this Amendment and Response.

If the Examiner believes any informalities remain in the application that may be corrected by Examiner's amendment, or there are any other issues that can be resolved by telephone interview, a telephone call to the undersigned agent at (404) 815-6102 is respectfully solicited.

Respectfully submitted,

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FIG. 4.

TAPPAHGVT*SAPDTRPAPGST*APPA (SEQ ID NO:1)

T* are O-glycosilated with N-acetyl-galactosamine